

ALTERATIONS IN MESOLIMBIC D3 AND MESOHIPOCAMPAL D2 RECEPTORS IN ELDERLY SCHIZOPHRENIA AND ALZHEIMER'S DISEASE

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The dopamine (DA) hypothesis of schizophrenia has been based largely on the evidence that pharmacological manipulations of the DA system either augment the symptoms or depress the symptoms of schizophrenia. This has been supported by an analysis of the effects of antipsychotics on the mesolimbic and nigrostriatal DA systems of animals, most notably, the rat. Again, reinforcing the hypothesis that it is the DA system innervating the striatum or nucleus accumbens (nigrostriatal and/or mesolimbic) that is most directly implicated in the pharmacological actions of these drugs. Direct studies of brains derived at post-mortem from schizophrenics have identified that one more more members of the D2 receptor family, the common site of action of antipsychotics, are elevated in density in the striatum of schizophrenics as compared to age-matched controls. In spite of the clinical efficacy of DA D2 antagonists, there is limited evidence in support of changes in D2 receptor number within the striatum being directly involved in the symptoms of schizophrenia. Recent findings have emphasized that other members of the D2 receptor family, the D3 and D4 receptor, may be altered in expression in schizophrenia. However, there are important interspecies differences in the anatomy of the mRNAs and receptor proteins for these receptors that are fundamental to the further elucidation of schizophrenia. In addition, nonstriatal or corticolimbic/mesohippocampal DA receptors, which are underdeveloped in the rat, are now known to evidence a high degree of differentiation in the human. Our results show that DA D2 receptors in the temporal lobe show an altered modular and laminar arrangement in schizophrenia. D3 receptors in the ventral striatum and ventral pallidum are elevated in patients off of neuroleptics but actively decreased by neuroleptics. In Alzheimer's disease patients there is a marked loss of D2 receptors in the temporal lobe and an elevation of D3 receptors in ventral striatum. The targets of the mesolimbic DA system is similarly affected in Alzheimer's disease and schizophrenia but the mesohippocampal D2 receptor system differs in these disorders .. Funding from US Federal Grants MH43880 and AG09215 and by an award from Scottish Rite Benevolent Foundation's Schizophrenia Research Program, N.M. J., U.S.A